

added by this amendment. In view of the following remarks, Applicants respectfully request favorable reconsideration of this application, withdrawal of all outstanding grounds of rejection, and the issuance of a Notice of Allowance.

A. Status of the application

Claims 51-68 are pending in this application. Under item numbers 3 and 5 of the Office Action, the Examiner had referred to claims 51-86, whereas it should read claims 51-68. In the Office Action dated May 16, 1997, claims 51-68 were rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention. Claims 51-68 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. Claims 51, 53, 64-66 and 68 were rejected under 35 U.S.C. § 102(e) as being anticipated by Erlich *et al.* (U.S. Patent No. 5,310,893). Claims 52, 63, and 67 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Erlich *et al.*

B. The Rejection under 35 U.S.C. §112 (first paragraph).

1. The Rejection of claims 51-68

Claims 51-68 were rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention. To the extent that the rejections are applied to the pending amended claims, Applicants respectfully traverse and request reconsideration.

The Examiner has stated that the specification does not appear to provide support for the embodiment of reagents which are defined in terms of an extension product in the presence of an "inducing agent." In the interest of advancing prosecution of the present application, Applicants have amended claim 51 so as to delete the language objected to by the Examiner. In view of the amendment to independent claim 51 which replaces the

word “inducing” with polymerizing, Applicants respectfully submit that the rejection under 35 U.S.C. § 112, first paragraph may now be properly withdrawn.

C. The Rejection under 35 U.S.C. § 112 (Second paragraph)

1. The Rejection of claims 51-68

Claims 51-68 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. To the extent that the rejections are applied to the pending amended claims, Applicants respectfully traverse and request reconsideration.

The Examiner has identified an aspect of the claims that appeared indefinite. Independent claim 51 has been amended to address the concern raised by the Examiner. In view of the above amendment to claim 51 which replaces the word “inducing” with polymerizing, it is respectfully submitted that the rejection of the claims under 35 U.S.C. § 112, second paragraph may now be properly withdrawn.

2. The Rejection of claim 68

Claim 68 was rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. To the extent that the rejection is applied to the pending amended claims, Applicants respectfully traverse and request reconsideration.

The Examiner objected to the recitation of “wherein the oligonucleotide primer is hybridized to the target” because it was unclear as to whether the claimed reagent itself is present in a form in which it is hybridized to the target nucleic acid or if it is only a property of the claimed reagent that it is capable of hybridizing to the target nucleic acid adjacent to the predetermined position. It is respectfully submitted that the claims should be read through the eyes of one having ordinary skill in the art and in light of the specification. *United States v. Teletronics, Inc.*, 857 F2d 778, 786, 8 U.S.P.Q.2d 1217, 1223 (Fed Cir. 1988), cert. denied, 490 U.S. 1046 (1989). Claim 68 is dependent upon independent claim 51 and as such it correctly recites a limitation wherein the oligonucleotide detection primer *is* hybridized to the target nucleic acid polymer

immediately adjacent to the predetermined position. The Examiner will appreciate that independent claim 51 recites that the oligonucleotide detection primer is “capable of hybridizing to a region on the target nucleic acid polymer flanking the 3’ end of the predetermined position.”

In light of the foregoing, Applicants respectfully submit that the Examiner may withdraw the 35 U.S.C. § 112, second paragraph rejection of claim 68.

D. The Rejection under 35 U.S.C. § 102 (e)

1. The Rejection of claims 51, 53, 64-66, and 68

Claims 51, 53, 64-66 and 68 were rejected under 35 U.S.C. § 102(e) as being anticipated by Erlich *et al.* To the extent that the rejections are applied to the pending amended claims, Applicants respectfully traverse and request reconsideration.

The Examiner has concluded that “Erlich teaches primers useful for the amplification of target nucleic acids containing a variable nucleotide, such as a polymorphism/mutation. Erlich teaches that primers are generated which have the property of hybridizing to the nucleic acid 5’ to the nucleotide containing the variable nucleotide, so that extension of the 3’ end of the primer results in the addition of a nucleotide complementary to the variable nucleotide.” The Examiner goes on to state that “[I]n particular, Erlich teaches primers, for example primer “DB01,” which hybridize to the target nucleic acid so that the 3’ nucleotide of the primer is immediately adjacent to a variable nucleotide and extension of the primer results in the addition of a nucleotide complementary to a first or second nucleotide residue.”

Applicants respectfully wish to point out that the Examiner has apparently misunderstood the teaching of Erlich *et al.* reference. The Erlich *et al.* reference discloses a process for determining the genotype of an individual with respect to the alleles at the HLA DP locus which involves obtaining a sample of nucleic acid from the individual, and hybridizing the nucleic acids with a *panel* of probes which are specific for variant segments of DPalpha and DPbeta genes. The Erlich *et al.* reference discloses that the

probes used for the hybridization reaction span the regions encoding the polymorphic amino acid residues and are shown as having a length of about 18 nucleotides. The sequences in the probe that encode the polymorphic amino acid residues **must** be included within a probe for detecting the alleles that encode the designated segment (page 25, lines 20-27).

The Examiner appears to be confusing the amplification primers of the Erlich *et al.* reference with that of the SSO primers. Applicants wish to point out that the use of DB01 (a left side amplification primer) in conjunction with DB03 (a right side amplification primer) will allow *amplification* of a 294 bp region of the second exon of DPbeta. It is this 294 bp fragment which then serves as an SSO (sequence-specific oligonucleotide) probe for the detection of allele-specific variants. The central feature of the DP DNA typing method of Erlich *et al.* involves the identification of the HLA DP alleles present in the sample by analyzing the pattern of binding of a panel of SSO probes (for example, the SSO probe generated by the use of DB01 and DB03 amplification primers). The Erlich *et al.* reference merely employs the PCR method to generate the probe to be used for the subsequent hybridization step. This point is made clear on page 6, at lines 27-30 wherein Erlich *et al.* state that “[T]o facilitate practice of this preferred embodiment, the present invention provides primers useful in amplifying by PCR the HLA DP target region.”

Furthermore, the Erlich reference states that “[T]o detect and distinguish between DP alleles in a practicable and economic fashion, however, one must know the nucleotide sequence of the alleles. The Erlich reference also states that “[F]or example, the “DEAV” probes of the invention can be used as one primer of a primer pair to provide for allele-specific amplification of “DEAV” DPbeta alleles.” This necessarily implies that the probe (primer in this case) **contains** the known variant nucleotide(s). Finally, the Erlich *et al.* reference discloses that “[B]ecause of the dispersed nature of the variation between the DPbeta alleles, rarely is any one probe able to identify uniquely a specific DPbeta

allele. Rather, according to the methods of the present invention, the identity of an allele is inferred from the pattern of binding of a panel of probes (i.e. SSO probes DB10, DB27, etc.), with each individual probe of the panel specific for different segments of the HLA DP gene" (page 3, lines 41-48).

Thus, the Erlich *et al.* reference does not disclose the Applicant's invention as claimed. The Applicants' invention as claimed does not utilize a hybridization step with an SSO *probe containing the sequence variation* to determine if the nucleotide variation is present. Instead, in the present invention as claimed, the reagent, *i.e.*, the oligonucleotide detection step primer, is designed to hybridize to a segment of the target adjacent to the variable sequence to be detected. Accordingly, the detection step primer **must not** contain the variable nucleotide within the oligonucleotide sequence. In the present invention as claimed, the presence of the variable nucleotide is detected using a primer extension reaction with labeled nucleotides with the oligonucleotide detection primer being extended only if the added labeled nucleotide is complementary to the variable nucleotide. This is clearly not the case for the Erlich *et al.* reference because in the latter, the SSO probes *containing* the variant nucleotide are used for the hybridization reaction to infer the presence of the variant nucleotide.

In view of the above, Applicants respectfully submit that the 35 U.S.C. § 102(e) rejection of the claims as being anticipated by Erlich *et al.* may now be properly withdrawn.

E. Rejections under 35 U.S.C. § 103(a)

1. The Rejection of claims 52, 63, and 67

Claims 52, 63, and 67 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Erlich *et al.* (U.S. Patent No. 5,310,893). To the extent that the rejections are applied to the pending amended claims, Applicants respectfully traverse and request reconsideration.

As stated above, Applicants believe that the Examiner has misunderstood the teaching of the Erlich *et al.* reference. Erlich *et al.* does not teach or suggest the use of an oligonucleotide detection primer for detecting the presence of a specific nucleotide at a predetermined position in a target nucleic acid polymer. Instead, Erlich *et al.* discloses a method of typing the HLA DP genotype of an individual which uses SSO probes to detect the presence of variant segments of the DPalpha and DPbeta alleles. The Examiner appears to be focusing on the use of PCR with amplification primers in the Erlich *et al.* method to *amplify* the target region of a DP variant allele. However, the use of the amplification DB01 and DB03 primers does not directly determine the presence of a variant nucleotide. This is most apparent from Example 9, which discloses the use of the DB01 and DB03 primers to *first* amplify the target region of the second exon of the DPbeta alleles using the PCR technique (page 36, lines 8-14). The HLA DP genotypes of the amplified DNA samples are then determined with the use of the DB27, DB28, DB39, DB30, DB31, DB32, DB33, and DB35 SSO probes (page 36, lines 35-45). The Erlich *et al.* method requires the *subsequent step* of hybridization of the SSO probe generated from use of the DB01 and DB03 primers with a sample of nucleic acid from an individual whose HLA DP genotype is to be determined. One of ordinary skill in the art, following the teaching of Erlich *et al.* Would, thus, not have arrived at the claimed invention. Accordingly, the Erlich *et al.* reference neither teaches nor suggests the claimed invention.

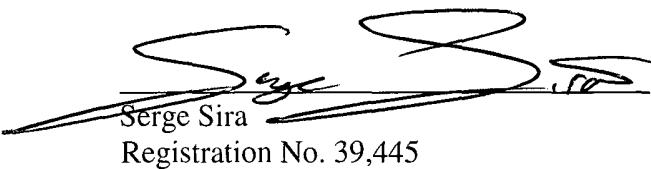
Furthermore, it is apparent that the Erlich *et al.* publication clearly teaches away from the instant invention because the SSO probe hybridization step is *not* employed in the invention as claimed. Applicants submit that those of ordinary skill in the art would not have had any motivation to modify the teaching of Erlich *et al.* so as to eliminate the SSO probe hybridization step. Moreover, those of ordinary skill would have presumed that the disclosed method in Erlich *et al.* would have set out the least number of steps and reagents thought necessary to accomplish the desired objective, and would have presumed

that an adverse reaction would have occurred if the disclosed method of Erlich *et al.* was not followed in the prescribed manner. *In re Freed*, 425 F. 2d 785, 165 U.S.P.Q. 570, 572 (C.C.P.A. 1970). Accordingly, Applicants submit that one of ordinary skill in the art would not have been motivated to eliminate any of the steps disclosed in Erlich *et al.*, especially that of the SSO hybridization step.

Accordingly, in view of Applicants' arguments that the Erlich *et al.* reference neither teaches nor suggests the claimed invention, Applicants therefore submit that claims 52, 63, and 67 are not obvious in view of the Erlich *et al.* reference. The teaching of Erlich *et al.* departs significantly from that of the claimed invention. For example, even if the DB01 or DB03 primer were to be labeled with a "capture" moiety so as to facilitate immobilization of the primer or amplified DNA (the SSO probes) on a solid support, one would still require the hybridization step of the SSO probe with that of a sample of nucleic acid from an individual whose HLA DP genotype is to be determined in order to practice the method of Erlich *et al.* In doing so, Erlich *et al.* necessarily do not arrive at the claimed invention because the invention as claimed does not employ a subsequent hybridization step with an SSO probe containing the variant sequence. Therefore, Erlich *et al.* teaches away from the use of an oligonucleotide detection primer comprising an attachment moiety as in the claimed invention. Applicants therefore submit that claims 52, 63, and 67 are not obvious in view of Erlich *et al.* Applicants respectfully submit that the 35 U.S.C. § 103(a) rejection of the claims may be properly withdrawn.

Having now fully responded to all of the rejections made by the Examiner,
Applicants respectfully submit that the present application is in condition for Allowance,
and earnestly solicit early notification of such favorable action.

Respectfully submitted,



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